Diabetes Pharmacology

Introduction

This lesson covers diabetes management, getting the blood glucose under control.

Type 1 diabetics must be treated with insulin because they make none. Their insulin regimens are complex and attempt to mirror what a healthy pancreas does. Diet and lifestyle are still important, but insulin is mandatory.

Type 2 diabetics may be treated with insulin, but only after non-insulin therapy fails. The main reason to avoid insulin in type 2 diabetics is that it causes weight gain, and type 2 diabetics already have insulin resistance. Diet and lifestyle modification are crucial for type 2 diabetics, prediabetics, and those with risk factors, specifically obesity. Reduction in calories ingested (diet), increase in calories spent (exercise), and making better food choices (nebulous and vague and not part of this lesson) can undo the damage done to the pancreas.

There are many drug mechanisms. A lot. This can be grueling to manage. Some are insulin, make more insulin, or sensitize insulin. Others eliminate sugar from the blood, help the patient eat less, or prevent glucose absorption from the gut.

Insulin Sensitizers

Insulin sensitization is a solution only for type 2 diabetics. Type 1 does not have the pathology of insulin insensitivity, so it would not benefit from sensitization.

Metformin is a biguanide. It is the only biguanide. Metformin is an amazing drug. We do not know how it works, but it works. Metformin runs the risk of **lactic acidosis** in **renal failure**, so metformin cannot be used in patients with chronic kidney disease and should be held when admitted to the hospital. Metformin causes **diarrhea** at the onset, but that diarrhea will abate with time. There is no titration of metformin. The goal is 1,000 mg twice daily. You start with 500 mg twice daily and let the patient have diarrhea. When the diarrhea stops, you go up to 1,000 mg twice daily, and let the patient have diarrhea. When the diarrhea stops, it won't come back. Metformin **sensitizes insulin**. Type 2 diabetes is caused by insulin insensitivity. Metformin resensitizes the system. It decreases hepatic glucose formation, allows for less insulin secretion, and therefore enables **weight loss and glucose control**—all without the risk of hypoglycemia.

This next part is for fun only. The most recent papers have implicated hepatic AMP-activated kinase as metformin's mechanism of action. We also know it has something to do with mTOR, and this pathway and that pathway. We do know that metformin does more than just sensitize insulin. Its effects are very similar to the *DAF-2* gene in the *C. elegans* worm. *DAF-2* mutants live longer and act younger for longer. In mice, *DAF-2* mutants lived 50% longer and were resistant to diabetes and even cancer. *DAF-2* is the equivalent of the insulin receptor and IGF-1 receptor in those species. Metformin's influence on health and disease goes beyond diabetes. Unintentionally discovered by looking at coronary artery disease patients, patients with diabetes on metformin were found to have less cardiovascular disease and fewer cancers than their matched counterparts. The link between age-related changes, metformin, and insulin is not well established. But there is a pretty good Explained episode on Netflix about it. End fun part.

Thiazolidinediones (**TZD**s, say "Tee Zee Dees") inhibit PPARγ ("Pee Par Gamma"). They are unrelated to metformin's mechanism of action, but also sensitize the system to insulin. This mostly occurs in adipocytes, where PPARγ increases GLUT4 expression and the storage of fatty acids as triglycerides. Therefore, TZDs induce adipocytes to take up extra glucose and store it away. PPARγ is required for adipocyte differentiation and survival and the insertion of GLUT4 transporters into the

adipocyte membrane. Adipose tissue is where PPARγ is most highly expressed, and the tissue with the most notable gene expression changes in response to treatment with PPARγ agonists. Therefore, the insulin-sensitizing effects, as well as certain negative side effects, of TZDs are generally attributed to adipose-specific PPARγ activation. In adipose tissue, PPARγ upregulates the expression of genes involved in glucose uptake and controls the expression of adipocyte-secreted factors, such as adiponectin, that communicate with other organs to affect whole-body insulin sensitivity.

But PPARγ is expressed in a lot of other places, too. We know that it **causes fluid retention** by influencing the collecting duct in ways we aren't sure of. Fluid retention in patients who have problems with volume overload (**heart failure**) can't use them. We know that PPARγ causes **weight gain** because it stimulates adipocytes to express GLUT4. PPARγ differentiates adipocytes. The stromal cells of mesenchyme can become adipocytes, osteoblasts, and fibroblasts; thus, it may not be surprising to learn that those cells also express PPARγ. PPARγ activation results in reduced osteoblast differentiation, nudging the stromal cells' differentiation towards adipocytes. This leads to an outpacing of osteoblasts by osteoclasts, leading to increased bone resorption and, therefore, **osteoporosis**. One TZD was thought to cause coronary artery disease. The media coverage and ensuing lawsuit gave all TZDs a bad name. Safety risks have had TZDs pulled from Europe, and caution is applied to their use in the United States. The restriction in the United States was removed in 2013. The FDA said it was safe to use TZDs, even in patients with pre-existing coronary artery disease. TZDs have shown a small risk of **bladder cancer**.

The main scenarios to avoid them are congestive heart failure (because fluid retention can provoke exacerbations) and those at risk for osteoporosis. But because weight gain only further exacerbates insulin desensitization, it may actually be detrimental to use TZDs. TZDs, like many of the drugs we have currently, were made in response to the identification of a molecular target for exploration. We grabbed a shotgun and took aim, hitting many targets we didn't mean to.

Stimulation of Insulin Release

Medications that release insulin cannot be used in type 1 diabetics because there are no β cells. Medications that release insulin will cause **weight gain** because insulin induces growth in all tissues, and there is a **risk of hypoglycemia** because insulin causes the blood sugar to fall. This is especially true in **renal failure** (acute renal failure in a patient on a stable dose more often than in someone with chronic kidney disease starting a medication) because the kidneys clear insulin. There are two classes in this category. Both classes are essentially the same medication and should not be combined. They both bind to and **close K^+ channels** that are normally closed by an increased concentration of high-energy molecules (ATP, NADH), resulting in pancreatic β cell depolarization.

These are the **sulfonylureas** and the **meglitinides**. The first-generation sulfonylureas are not seen anymore, ever, and we are not sharing their names with you. The second-generation sulfonylureas were the go-to medication after metformin for a decade. Now, the ADA does not dictate which agent to start as the second, though in your practice pattern, you should consider sulfonylureas as THE right choice after metformin, except where contraindicated. The second-generation sulfonylureas are **glyburide** and **glipizide**.

The meglitinides represent a rarely used class because the sulfonylureas were around first, and other classes have been discovered after, making the meglitinides superfluous. They all have the suffix -glinide: repaglinide, nateglinide, mitiglinide.

Incretin Pathway

The incretin GLP-1 is a short-lived molecule with a short half-life. The enzyme DPP-4 degrades it. The discovery of this pathway opened the door for novel medications that focus on the pancreas, so it can be used only in type 2 diabetics. The GI tract releases GLP-1 in response to a meal. It prepares the pancreas for the coming glucose, even before the glucose arrives. It also **satiates hunger**. The GLP-1 agonists and DPP-4 inhibitors were so promising that they got A LOT of attention. The ADA even recommended GLP-1 agonists to be used before insulin, deviating from the "use whatever you want" plan they had. Weight loss, no hypoglycemia, and A1c control. This pathway was our salvation! Then we used them, and what we thought of as amazing might not be so grand. There are three possible outcomes in the next decade for this pathway: we'll figure out more about the pathway and start doing it right (fewer side effects), their use will demonstrate a lower risk of side effects than initially encountered, or these classes will generate such severe complications that they will be pulled from the market.

GLP-1 analogs are **injectable** medications that act as GLP-1, only with a sustained signal. Some of these analogs last so long they need to be injected only once a week. These medications have become a source of contention. The ADA recommends two oral medications, and if more glucose control is required, the addition of a GLP-1 analog. They are injectable, like insulin. But unlike insulin, they **do not cause weight gain**. Because metabolic syndrome is at the heart of type 2 diabetes, and weight gain only promotes more insulin insensitivity, the concept of "injectable and weight loss" sounds better than "injectable and weight gain." In addition, the injection frequency is less with GLP-1 analogs (once a day or once a week) than insulins (as infrequently as once per day, but often more than that). Sounds awesome, right? **GLP-1 analogs cause pancreatitis** and **pancreatic cancer**. So, in a patient with type 2 diabetes who needs a third agent to control their blood sugar, use a GLP-1 analog. If ever they suffer abdominal pain, pancreatitis, or any symptom of the GI tract, stop the GLP-1 analog. GLP-1 analogs are **better injectables than insulin** because insulin causes weight gain and feeds forward the problems associated with metabolic syndrome as well as the risk of hypoglycemia. GLP-1 analogs cause weight loss and don't cause hypoglycemia.

The 2018 ADA national meeting had a day dedicated to GLP-1 presentations. The morning sessions were about how amazing GLP-1 analogs worked: weight loss, A1c control, patient compliance. The afternoon sessions were about how all the GLP-1 analogs' success during clinical trials was not seen outside of the controlled setting, and that the rate of side effects precluded their use. The morning said these drugs were the best thing since Betty White (who was alive before sliced bread). The afternoon said they weren't worth the risk of complications and side effects. The tacit takeaway (stating it explicitly would compromise the researchers' integrity, which is not our intention, either) was that pharma-funded clinical trials showed an obvious benefit, whereas patient-funded utilization of the drugs in real life didn't.

DPP-4 inhibitors, the "gliptins" (saxagliptin, sitagliptin), are **oral** agents that prevent the degradation of endogenous incretins. No injections! Same system! W00t! In 2018, a meta-analysis found there to be no benefit in all-cause mortality, heart attack, or stroke. Wh00ps? They, like all oral medications, tend to lower the A1c by about one percent. Like the GLP-1 analogs (because DPP-4 inhibitors increase endogenous GLP-1), DPP-4 inhibitors have been associated with **pancreatitis** and **pancreatic cancer**. Wh00aaaat?! With the risk high, and the benefit essentially nonexistent, you should not ever prescribe this drug class.

The content in this section hints at our limited understanding of the incretin system and its effects on the pancreas. Yes, increased incretins will stimulate insulin and prevent glucagon release. Both of these things decrease blood sugar. This makes for an excellent slide in a presentation at a national conference or in a sales demonstration. But obviously, with the rates of pancreatitis and pancreatic cancer increasing as we use and study these drugs more, there must be some unintended consequence in signaling that we either do not understand or have not elucidated. GLP-1s' benefit may be as simple as helping obese overeaters eat less.

The ADA recommends that if the patient has **heart disease** or **chronic kidney disease,** either a GLP-1 or SGLT-2 inhibitor should be chosen as the second agent because there are cardiovascular health benefits. What those two drugs have in common is the absence of weight gain.

Medications That Reduce Total Body Sugar

These are either the best medications ever or the worst ideas ever. But because they actually get sugar out of the body, and not just stuff it somewhere other than the bloodstream, these medications feel like they should work the best.

SGLT-2 inhibitors. Do you remember what causes a patient with type 2 diabetes to go into HHS? How about the treatment of DKA? Blood sugar exceeds the reabsorption capacity of the proximal convoluted tubule, and glucosuria causes an osmotic shift leading to dehydration. When you diagnose someone with HHS, you BOMB them with fluids. Yes, the hyperglycemia is a problem. But what is killing the patient right now is volume depletion. Now, what if you reduced the kidneys' ability to reabsorb glucose? Ooh, glucose would leave the body! Yay! We can reduce blood sugar by having it be urinated out. What a cool idea. Hmmm. Wonder if there could be any unintended consequences? As in, say, I dunno, causing osmotic diuresis leading to volume depletion and dehydration? You know, like what hyperglycemia does in a normal kidney? Yeah . . . **SGLT-2 inhibitors cause euglycemic HHS**. But wait. Because patients with type 1 diabetes have kidneys and SGLT-2 inhibitors work on the kidney, not the pancreas, we can use this oral medication to treat type 1 diabetics! Hooray! Oh . . . but wait . . . **SGLT-2 inhibitors cause euglycemic DKA**.

When this medication's mechanism of action was announced in a television commercial, Dr. Williams could not believe his ears. In the several years following that advertisement, he reported a dozen cases of SGLT-2-induced euglycemic DKA. The pharmaceutical representatives at the ADA convention knew him by name before he approached the booth. Not because of OnlineMedEd, but because he was the guy with all the case reports published by residents about how terrible these medications are. When asked what he should teach residents about this drug class, both pharmaceutical companies (each the other's competitor) gave him the FDA insert in response. You will see advertisements for this drug class. It was pushed through the FDA under the "we need to fix diabetes" program (not its real name). It is being combined with other medications to create "new" (i.e., patentable) drugs, and is sold under the guise, "one pill, two medications." This is obviously our founder's bias, but the ludicrous mechanism of action and the frequent complications make this drug class the worst idea ever. **Never use this drug class.** It makes teleologic sense—get rid of glucose from the body. But never before was euglycemic DKA a subject to teach. Many authors state that this drug class is worth the risk because it is a predictable and easily treatable condition. *The EMPA-REG trial showed that SGLT-2 inhibitors were better* ***than placebo*** *(not another already established diabetes treatment) at improving glucose control and reducing cardiovascular disease. The problem with this study is that, although significant, the improvements were always single-digit percent changes, most of them under 1%. The study didn't report on side effects (like euglycemic DKA). A treatment was better than no treatment. No kidding! We at OME believe that this woefully overstates their utility and grossly understates their danger. SGLT-2 inhibitors are, in effect, diuretics, so they should help heart failure patients who need diuretics. That's it.*

Acarbose. The enterocytes use α-galactosidase to digest disaccharides into monosaccharides. Only monosaccharides can be absorbed by the enterocyte. So, if a medication is added to the lumen of the gut that prevents sugars from being digested into monomers, the sugar cannot be absorbed. Hooray! Let the diabetics feast on carbs! All they need do is take this medication, and they won't be absorbed! We stop the problem even before it gets into their body! Hrmm . . . where did we hear about the consequences of not absorbing ingested substances? Oh. Right. Diarrhea. When an osmotically active substance is ingested but not absorbed, water leaves the body into the lumen to balance the osmotic force. As long

as that not-absorbed substance is not fat (fat malabsorption has additional consequences), the person experiences **osmotic diarrhea**. So although acarbose is a drug class that exists, using a medication that intentionally causes osmotic diarrhea doesn't sound like a very good idea if you care about patient compliance. Although it's not as dangerous as SGLT-2 inhibitors, you should also never use this medication. The good news is you won't be pressured to—patients don't want diarrhea, and the drug is so old that it isn't advertised on TV.

Summarizing Non-Insulins

DRUG	MECHANISM	WEIGHT CHANGE	HYPOGLYCEMIA RISK	NOTES
Biguanides *Metformin*	Insulin sensitizer	Loss	No	Lactic acidosis Precluded CKD
Sulfonylureas *Glyburide, glipizide*	K^+-channel blocker Release insulin	Increase	Yes	Caution CKD
TZDs *-glitazones*	PPARγ activation (adipose uptake)	Increase	No	Fluid retention Precluded CHF
GLP-1s *-tinides*	GLP-1 agonist	Decrease	No	Pancreatitis, pancreatic cancer
DPP-4 inhibitors *-gliptins*	Inhibit endogenous incretin degradation	No change	No	Pancreatitis, pancreatic cancer
SGLT-2 inhibitors *-gliflozin*	Block glucose reabsorption in PCT	No change	No	Cause euglycemic DKA, dehydration, are actually diuretics
α-galactosidase inhibitors *Acarbose*	Prevent digestion of small carbohydrates at the brush border	No change	No	Diarrhea precludes their use

Table 3.1: Non-insulins

Adding Insulin to a Type 2 Regimen

Always start with long-acting basal insulin first. Escalation will be in dosage, frequency of finger sticks, number of meals, etc. This addition of insulin is far more Clinical than Basic Science, so the discussion of dosing and escalation is not covered here. It will be covered in the Clinical Sciences. If you want a preview of things to come, check out the Intern Content's *Inpatient Diabetes* lesson.

Insulins

The normal pancreas secretes a certain amount of insulin all the time. The whole business about glucagon-dominant vs. insulin-dominant was taught to you, by us, as being polar opposites—either there was glucagon, or there was insulin. But the phrase we used was insulin-*dominant*, not insulin-*only*. That is because there is always a bit of insulin around. In the fasting state, glucagon wins, and the liver makes glucose for the rest of the body. But in truth, there is always some insulin being secreted. This is called the **basal insulin**. When a healthy patient eats a meal, incretins prepare the pancreas, and rising

blood glucose triggers insulin release. The insulin rises as the blood sugar rises and falls as the blood sugar falls back to normal. This mealtime insulin boost, this **prandial insulin** increase, this **bolus of insulin** that occurs with meals, is in addition to the basal insulin that exists all the time.

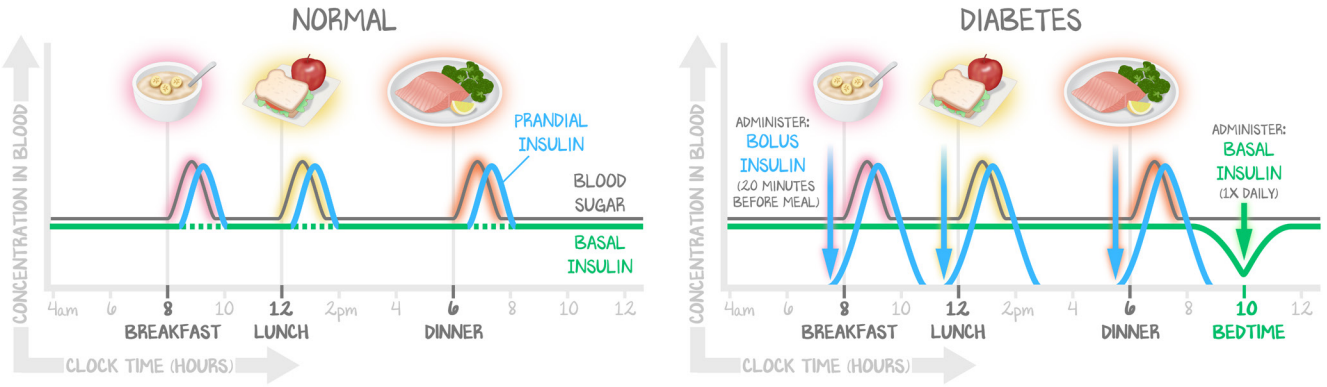

Figure 3.1: Insulin in Diabetes
The normal pancreas has basal insulin around all the time. The pancreas acts as a glucose sensor and responds to changes in glucose by releasing insulin. Because a type 1 diabetic has no pancreas to either act as a sensor or produce insulin, the injection of insulin should be timed such that the insulin peaks at the right time and the right level to accommodate the meal. Because insulin takes time to be absorbed, that means insulin must be administered prior to the meal. The best insulin administration is based on the food about to be consumed, though most patients simply take a fixed dose.

The best control of blood sugar comes from matching what a healthy pancreas would do—**basal bolus**. A basal insulin (aka long-acting) is given once a day (often at night). Throughout the day, rapid-acting bolus insulin is given before mealtimes. We will not be talking about how to dose insulin; that comes in clinical. We're talking only about the concept here, as this will streamline your memorization of the insulins. The key fundamental principle that most people involved with diabetes in any way (providers and patients) fail to understand is that the insulin that a person is injecting right now is for the **meal they are about to eat** and is NOT based on the blood sugar they have right now. A patient measures their blood sugar 30 minutes before a meal. A patient should inject insulin 15–20 minutes before a meal. The patient eats the meal. The insulin in their subcutaneous fat diffuses into the bloodstream such that as the meal enters their veins, the insulin is ready to act. If a patient measures their blood sugar 30 minutes before a meal, and it is elevated, it means that the amount of insulin they gave themselves at the last meal was too little for the food they ate. They can't go back in time and add insulin to the previous meal, but they can make up the difference now. Additional **correctional** insulin can be **added to the mealtime insulin**.

Basal insulins are long-acting insulins. The long-acting insulins are **glargine**, **detemir**, **degludec**. As Dr. Williams does in the video, say them out loud, sing-song. No "and" before degludec. They are all the same, completely interchangeable. Glargine was first. To get detemir patented, it billed itself as the twice-daily long-acting medication. Glargine = detemir = degludec. Consider them the same, used the same way, only chosen by which one is covered by the formulary. There are differences, and the ADA ranks them. Practically, a patient's insurance will have one on formulary; use that one for that one patient. In 2019 there was a lawsuit against the pharmaceutical companies who make these drugs. The suit used RICO laws, laws invented to bust the mob. Pharma was literally price gouging patients and paying middlemen (Pharmacy Benefits Managers, PBMs) kickbacks to keep prices high.

Bolus insulins are short-acting insulins. They are absorbed quickly and act for a short amount of time. The best are absorbed in less than 30 minutes and turn off at 4 hours. The rapid-acting, prandial, or bolus insulins are **aspart** and **lispro** (and glulisine). "Aspart and Lispro; Glargine Detemir Degludec."

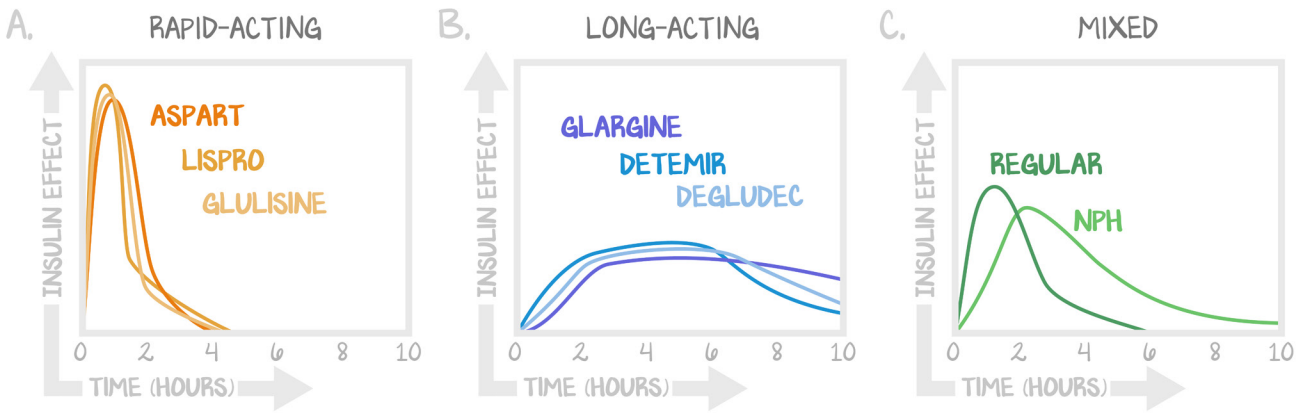

Figure 3.2: Insulin
There are three types of insulin. There is rapid-acting prandial insulin, which is rapid on, rapid off. Rapid-acting insulin includes the medications aspart, lispro, glulisine. There is long-acting basal insulin, which is injected once a day. Long-acting insulin includes the medications glargine, detemir, degludec. Mixed insulin is a combination of NPH and regular. The only time regular insulin should be used on its own is in an insulin pump administered as a continuous infusion with prandial boluses.

Regular insulin and **NPH insulin** were first. Regular insulin is absorbed over 30 minutes and lasts 6 hours. It is an abysmal rapid insulin. NPH provides basal coverage, but only for 12 hours. In terms of the sophistication we have developed in matching the normal pancreas' behavior, these insulins seem like they have no place. Indeed, when a patient is willing and able to perform basal-bolus regimens, the basal-prandial insulins should be used. But there are times when that isn't the case. For example, patients **without insurance** cannot afford basal-bolus. Generic regular insulin and NPH insulin are all they have. And so a semi-basal-bolus regimen can be devised, with NPH twice a day and regular insulin with meals. Two different insulins, two different vials, at least five injections a day. A recipe for disaster. Instead, pharma did something good—pharma **mixed insulins**. The premade mixed insulins are named for their proportion of NPH and regular; thus, a 70/30 premade mixed insulin is 70% NPH and 30% regular. This allows for **twice-daily injections** of "one insulin." To the patient, it is one vial and gets one dose. There is no correction, there is no calculating carbs, there isn't even the need to check the blood sugar. This is obviously inferior to basal-bolus with correction, but it is a regimen that can be utilized in people who are unwilling or unable to do basal-bolus. It's also ideal for the elderly, in whom the A1c control can be more liberal. Basal-bolus requires a committed patient, willing to stab themselves with a needle four or five times a day and prick their finger the same number of times, every day. Mixed insulin affords two injections a day, no calculations, and the liberty to not check the sugar. The trade-off? Mixed insulins tend not to lower the A1c as well as basal-bolus.

Insulins can come in **vials**, in which the patient will need to draw up the correct amount of insulin. This requires dexterity and good vision, things that are compromised by severe diabetes. **Insulin pens** have made a huge impact on those for whom vials were burdensome or too difficult. The pen is adjusted to the right number of units (clearly displayed in a window, rather than having to look at a meniscus in a syringe), a needle is added to the tip, and it is then pressed into the subcutaneous fat and thumb injected. **Insulin pumps** are very sophisticated devices best used by type 1 diabetics. Most type 2 diabetics do not require this level of sophistication or even require injections with every meal. An insulin pump uses regular insulin and infuses a basal rate of regular insulin all the time. If ever the patient determines they need additional insulin, they can select the insulin bolus to be administered in addition to the basal rate. **Insulin pumps use regular insulin.** With **continuous glucose monitoring**, a patient can now monitor and titrate insulin at any time interval they choose. Insulin pumps must be worn and are continuously connected to the subQ space. Continuous glucose monitoring must remain connected to the subQ space. So, although it is the best method for using insulin, it isn't the most convenient.

Blood Sugar Goal

The ACCORD trial said that if you try to get a patient's blood sugar to normal ranges with insulin, you cause more harm than good. This was true then. The goal with insulin is to get the A1c below 7 and the premeal blood sugar between 70 and 120 mg/dL. You must learn this fact and regurgitate it. **Too strict control causes hypoglycemia.** Having heard this, the response by most providers is to fear insulin, not titrate fast enough, and be satisfied with suboptimal glucose control. The ACCORD study was done when we did not have insulin pumps, continuous glucose monitoring, **or even iPhones** (the first iPhone came out in 2007; the ACCORD trial *was published* in 2008). Patients in the study were given instructions and sent out the door. Between clinic visits, they had to do everything on their own: check sugar, calculate dose, give dose. And what do you know? Patients did it wrong. You know why? Because insulin is really hard to figure out. And if the patient overdoes it once, just once, they can die of hypoglycemia. But now, 15 years later with a plethora of mobile apps, instant connection to physicians on-demand, and advancing technology in glucose monitoring and insulin delivery, the risk of symptomatic hypoglycemia seen in the ACCORD trial can be vastly reduced. Educating patients to count carbs, calculate their insulin dose based on the meal and correction, the speed of onset of insulins, etc., also allow for better glucose control without the increased risk. But because it was such a landmark trial, everyone perpetuates a finding without considering why that finding was there. Because there had been demonstrable reductions in microvascular and macrovascular complications with strict blood glucose control before the ACCORD trial, and the only negative consequence of the ACCORD trial was overdoing the insulin, we expect alterations in the recommendations as technology continues to improve.

Getting the A1c below 8 substantially reduces the risk of vascular disease.
Getting the A1c below 7 is the federal quality metric goal.
Getting the A1c below 6 caused poorer outcomes in the ACCORD trial, but that doesn't mean patients who are savvy with their disease and have the tools to control it better shouldn't do that.